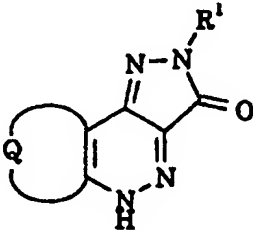




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>6</sup> : <b>C07D 487/04, A61K 31/50 // (C07D 487/04, 237:00, 231:00)</b></p>	<p><b>A1</b></p>	<p>(11) International Publication Number: <b>WO 99/00391</b> (43) International Publication Date: 7 January 1999 (07.01.99)</p>
<p>(21) International Application Number: PCT/GB98/01774 (22) International Filing Date: 17 June 1998 (17.06.98) (30) Priority Data: 9713707.9 27 June 1997 (27.06.97) GB (71) Applicant (for all designated States except US): MERCK SHARP &amp; DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BLURTON, Peter [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). FLETCHER, Stephen, Robert [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). (74) Agent: THOMPSON, John; Merck &amp; Co., Inc., European Patent Dept., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> With international search report.</p>
<p>(54) Title: TRICYCLIC PYRAZOLO-PYRIDAZINONE ANALOGUES AS GABA-A RECEPTOR LIGANDS</p> <div style="text-align: center;">  <p>(I)</p> </div> <p>(57) Abstract</p> <p>A class of pyrazolo[4,3-c]pyridazin-3-one analogues of formula (I), substituted at the 2-position by an optionally substituted aryl or heteroaryl moiety, and wherein the pyridazine ring of the pyrazolo-pyridazinone ring system is fused to an alkylene chain, are selective ligands for GABA<sub>A</sub> receptors, in particular having affinity for the <math>\alpha 2</math> and/or <math>\alpha 3</math> subunit thereof, and are accordingly of benefit in the treatment and/or prevention of disorders of the central nervous system, including anxiety and convulsions.</p>		

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**TRICYCLIC PYRAZOLO-PYRIDAZINONE ANALOGUES AS**  
**GABA-A RECEPTOR LIGANDS**

The present invention relates to a class of fused tricyclic compounds  
5 based on a substituted pyrazolo-pyridazine moiety, and to their use in  
therapy. More particularly, this invention is concerned with tricyclic  
pyrazolo[4,3-c]pyridazin-3-one analogues which are ligands for GABA<sub>A</sub>  
receptors and are therefore useful in the therapy of deleterious mental  
states.

10 Receptors for the major inhibitory neurotransmitter, gamma-  
aminobutyric acid (GABA), are divided into two main classes: (1) GABA<sub>A</sub>  
receptors, which are members of the ligand-gated ion channel superfamily;  
and (2) GABA<sub>B</sub> receptors, which may be members of the G-protein linked  
receptor superfamily. Since the first cDNAs encoding individual GABA<sub>A</sub>  
15 receptor subunits were cloned the number of known members of the  
mammalian family has grown to include at least six  $\alpha$  subunits, four  $\beta$   
subunits, three  $\gamma$  subunits, one  $\delta$  subunit, one  $\epsilon$  subunit and two  $\rho$   
subunits.

Although knowledge of the diversity of the GABA<sub>A</sub> receptor gene  
20 family represents a huge step forward in our understanding of this ligand-  
gated ion channel, insight into the extent of subtype diversity is still at an  
early stage. It has been indicated that an  $\alpha$  subunit, a  $\beta$  subunit and a  $\gamma$   
subunit constitute the minimum requirement for forming a fully  
functional GABA<sub>A</sub> receptor expressed by transiently transfecting cDNAs  
25 into cells. As indicated above,  $\delta$ ,  $\epsilon$  and  $\rho$  subunits also exist, but are  
present only to a minor extent in GABA<sub>A</sub> receptor populations.

Studies of receptor size and visualisation by electron microscopy  
conclude that, like other members of the ligand-gated ion channel family,  
the native GABA<sub>A</sub> receptor exists in pentameric form. The selection of at  
30 least one  $\alpha$ , one  $\beta$  and one  $\gamma$  subunit from a repertoire of seventeen allows  
for the possible existence of more than 10,000 pentameric subunit

combinations. Moreover, this calculation overlooks the additional permutations that would be possible if the arrangement of subunits around the ion channel had no constraints (i.e. there could be 120 possible variants for a receptor composed of five different subunits).

5            Receptor subtype assemblies which do exist include, amongst many others,  $\alpha 1\beta 2\gamma 2$ ,  $\alpha 2\beta 2/3\gamma 2$ ,  $\alpha 3\beta 2/3$ ,  $\alpha 2\beta \gamma 1$ ,  $\alpha 5\beta 3\gamma 2/3$ ,  $\alpha 6\beta \gamma 2$ ,  $\alpha 6\beta \delta$  and  $\alpha 4\beta \delta$ . Subtype assemblies containing an  $\alpha 1$  subunit are present in most areas of the brain and are thought to account for over 40% of GABA<sub>A</sub> receptors in the rat. Subtype assemblies containing  $\alpha 2$  and  $\alpha 3$  subunits respectively  
10 are thought to account for about 25% and 17% of GABA<sub>A</sub> receptors in the rat. Subtype assemblies containing an  $\alpha 5$  subunit are expressed predominantly in the hippocampus and cortex and are thought to represent about 4% of GABA<sub>A</sub> receptors in the rat.

            A characteristic property of all known GABA<sub>A</sub> receptors is the  
15 presence of a number of modulatory sites, one of which is the benzodiazepine (BZ) binding site. The BZ binding site is the most explored of the GABA<sub>A</sub> receptor modulatory sites, and is the site through which anxiolytic drugs such as diazepam and temazepam exert their effect. Before the cloning of the GABA<sub>A</sub> receptor gene family, the  
20 benzodiazepine binding site was historically subdivided into two subtypes, BZ1 and BZ2, on the basis of radioligand binding studies. The BZ1 subtype has been shown to be pharmacologically equivalent to a GABA<sub>A</sub> receptor comprising the  $\alpha 1$  subunit in combination with a  $\beta$  subunit and  $\gamma 2$ . This is the most abundant GABA<sub>A</sub> receptor subtype, and is believed to  
25 represent almost half of all GABA<sub>A</sub> receptors in the brain.

            Two other major populations are the  $\alpha 2\beta \gamma 2$  and  $\alpha 3\beta \gamma 2/3$  subtypes. Together these constitute approximately a further 35% of the total GABA<sub>A</sub> receptor repertoire. Pharmacologically this combination appears to be equivalent to the BZ2 subtype as defined previously by radioligand  
30 binding, although the BZ2 subtype may also include certain  $\alpha 5$ -containing subtype assemblies. The physiological role of these subtypes has hitherto

been unclear because no sufficiently selective agonists or antagonists were known.

It is now believed that agents acting as BZ agonists at  $\alpha 1\beta\gamma 2$ ,  $\alpha 2\beta\gamma 2$  or  $\alpha 3\beta\gamma 2$  subunits will possess desirable anxiolytic properties. Compounds which are modulators of the benzodiazepine binding site of the GABA<sub>A</sub> receptor by acting as BZ agonists are referred to hereinafter as "GABA<sub>A</sub> receptor agonists". The  $\alpha 1$ -selective GABA<sub>A</sub> receptor agonists alpidem and zolpidem are clinically prescribed as hypnotic agents, suggesting that at least some of the sedation associated with known anxiolytic drugs which act at the BZ1 binding site is mediated through GABA<sub>A</sub> receptors containing the  $\alpha 1$  subunit. Accordingly, it is considered that GABA<sub>A</sub> receptor agonists which interact more favourably with the  $\alpha 2$  and/or  $\alpha 3$  subunit than with  $\alpha 1$  will be effective in the treatment of anxiety with a reduced propensity to cause sedation. Also, agents which are antagonists or inverse agonists at  $\alpha 1$  might be employed to reverse sedation or hypnosis caused by  $\alpha 1$  agonists.

The compounds of the present invention, being selective ligands for GABA<sub>A</sub> receptors, are therefore of use in the treatment and/or prevention of a variety of disorders of the central nervous system. Such disorders include anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, animal and other phobias including social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic and acute stress disorder, and generalized or substance-induced anxiety disorder; neuroses; convulsions; migraine; depressive or bipolar disorders, for example single-episode or recurrent major depressive disorder, dysthymic disorder, bipolar I and bipolar II manic disorders, and cyclothymic disorder; psychotic disorders including schizophrenia; neurodegeneration arising from cerebral ischemia; attention deficit hyperactivity disorder; and disorders of circadian rhythm, e.g. in subjects suffering from the effects of jet lag or shift work.

Further disorders for which selective ligands for GABA<sub>A</sub> receptors may be of benefit include pain and nociception; emesis, including acute, delayed and anticipatory emesis, in particular emesis induced by chemotherapy or radiation, as well as post-operative nausea and vomiting; eating disorders including anorexia nervosa and bulimia nervosa; muscle spasm or spasticity, e.g. in paraplegic patients; and hearing loss. Selective ligands for GABA<sub>A</sub> receptors may also be effective as pre-medication prior to anaesthesia or minor procedures such as endoscopy, including gastric endoscopy.

US-4591589 and GB-A-2166439 describe various classes of substituted pyrazolo[4,3-*c*]cinnolin-3-one derivatives. The compounds described in GB-A-2166439 are stated to be useful as psychotropic agents. The compounds described in US-4591589 are stated to be useful for relieving anxiety. There is, however, no disclosure nor any suggestion in either of these publications of the compounds according to the present invention wherein the pyridazine ring of a pyrazolo[4,3-*c*]pyridazin-3-one moiety is fused to an alkylene chain.

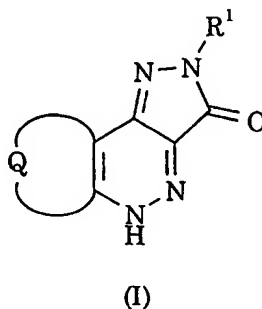
US Patent No. 4,602,014 relates to a family of substituted pyrazolo[3,4-*d*]pyridin-3-one derivatives wherein the pyridine ring thereof is fused *inter alia* to an alkylene chain. These compounds are stated therein to be benzodiazepine receptor ligands having nervous system regulatory activity, including anxiomodulating activity. However, there is no disclosure nor any suggestion anywhere in US Patent No. 4,602,014 of the fused tricyclic pyrazolo[4,3-*c*]pyridazin-3-one analogues in accordance with the present invention.

The present invention provides a class of tricyclic pyrazolo-pyridazine analogues which possess desirable binding properties at various GABA<sub>A</sub> receptor subtypes. The compounds in accordance with the present invention have good affinity as ligands for the  $\alpha 2$  and/or  $\alpha 3$  subunit of the human GABA<sub>A</sub> receptor. The compounds of this invention may interact more favourably with the  $\alpha 2$  and/or  $\alpha 3$  subunit than with the

$\alpha 1$  subunit. Desirably, the compounds of the invention will exhibit functional selectivity in terms of a selective efficacy for the  $\alpha 2$  and/or  $\alpha 3$  subunit relative to the  $\alpha 1$  subunit.

The compounds of the present invention are GABA<sub>A</sub> receptor  
5 subtype ligands having a binding affinity ( $K_i$ ) for the  $\alpha 2$  and/or  $\alpha 3$  subunit, as measured in the assay described hereinbelow, of 100 nM or less, typically of 50 nM or less, and ideally of 10 nM or less. The compounds in accordance with this invention may possess at least a 2-fold, suitably at least a 5-fold, and advantageously at least a 10-fold, selective  
10 affinity for the  $\alpha 2$  and/or  $\alpha 3$  subunit relative to the  $\alpha 1$  subunit. However, compounds which are not selective in terms of their binding affinity for the  $\alpha 2$  and/or  $\alpha 3$  subunit relative to the  $\alpha 1$  subunit are also encompassed within the scope of the present invention; such compounds will desirably exhibit functional selectivity in terms of a selective efficacy for the  $\alpha 2$   
15 and/or  $\alpha 3$  subunit relative to the  $\alpha 1$  subunit.

The present invention provides a compound of formula I, or a salt or prodrug thereof:



20

wherein

Q represents  $-(CH_2)_n-$ ;

n is 3, 4, 5 or 6; and

R<sup>1</sup> represents aryl or heteroaryl, either of which groups may be  
25 optionally substituted.

The group R<sup>1</sup> may be unsubstituted or substituted by one or more, preferably one or two, substituents. Examples of optional substituents on the group R<sup>1</sup> include C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, aryl, aryl(C<sub>1-6</sub>)alkyl, C<sub>3-7</sub> heterocycloalkyl, heteroaryl, heteroaryl(C<sub>1-6</sub>)alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulphonyl, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub>)alkylamino, C<sub>2-6</sub> alkylcarbonyl, C<sub>2-6</sub> alkoxy carbonyl, halogen, cyano and trifluoromethyl.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

As used herein, the expression "C<sub>1-6</sub> alkyl" includes methyl and ethyl groups, and straight-chained or branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, *n*-propyl, isopropyl, isobutyl, *tert*-butyl and 2,2-dimethylpropyl. Derived expressions such as "C<sub>1-6</sub> alkoxy", "C<sub>1-6</sub> alkylthio", "C<sub>1-6</sub> alkylsulphonyl" and "C<sub>1-6</sub> alkylamino" are to be construed accordingly.

The expression "C<sub>2-6</sub> alkenyl" as used herein refers to straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl, allyl and dimethylallyl groups.



The expression "C<sub>2-6</sub> alkynyl" as used herein refers to straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

Particular C<sub>3-7</sub> cycloalkyl groups include cyclopropyl and cyclohexyl.

5 Particular aryl groups include phenyl and naphthyl.

Particular aryl(C<sub>1-6</sub>)alkyl groups include benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

Suitable heterocycloalkyl groups include azetidiny, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl groups.

10 Suitable heteroaryl groups include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl groups.

15 The expression "heteroaryl(C<sub>1-6</sub>)alkyl" as used herein includes furylmethyl, furylethyl, thienylmethyl, thienylethyl, oxazolylmethyl, oxazolylethyl, thiazolylmethyl, thiazolylethyl, imidazolylmethyl, imidazolylethyl, oxadiazolylmethyl, oxadiazolylethyl, thiadiazolylmethyl, thiadiazolylethyl, triazolylmethyl, triazolylethyl, tetrazolylmethyl, 20 tetrazolylethyl, pyridinylmethyl, pyridinylethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolinylmethyl and isoquinolinylmethyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine.

25 The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible *in vivo* into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in *Design of Prodrugs*, ed. H. 30 Bundgaard, Elsevier, 1985.

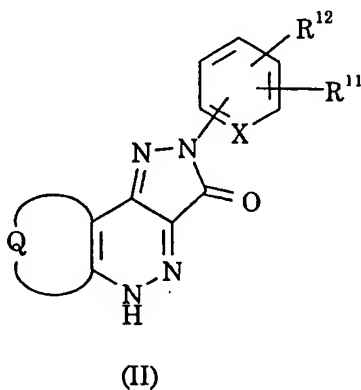
Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

Suitably, Q represents  $-(CH_2)_n-$  in which n is 4 or 5.

Suitably, the group  $R^1$  represents phenyl or pyridinyl, either unsubstituted or substituted by one or more optional substituents selected typically from  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy and halogen.

Particular values of  $R^1$  include phenyl, methylphenyl, dimethylphenyl, ethylphenyl, isopropyl-phenyl, methoxyphenyl, ethoxyphenyl, fluorophenyl, difluoro-phenyl, chlorophenyl, pyridinyl and methylpyridinyl.

A particular sub-class of compounds according to the invention is represented by the compounds of formula II, and salts and prodrugs thereof:



wherein

Q is as defined above with reference to formula I;

X represents CH or nitrogen; and

R<sup>11</sup> and R<sup>12</sup> independently represent hydrogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylsulphonyl, C<sub>2-6</sub> alkylcarbonyl, halogen, cyano or trifluoromethyl.

Suitably, R<sup>11</sup> represents hydrogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy or halogen.

5 Particular values of R<sup>11</sup> include hydrogen, methyl, ethyl, isopropyl, methoxy, ethoxy, fluoro and chloro.

Suitably, R<sup>12</sup> represents hydrogen, C<sub>1-6</sub> alkyl or halogen. Particular values of R<sup>12</sup> include hydrogen, methyl and fluoro, especially hydrogen.

Specific compounds within the scope of the present invention

10 include:

- 2-(4-methoxyphenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;
- 2-(4-fluorophenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;
- 2-(4-methylphenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;
- 2-(3-chlorophenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;
- 15 2-(2-fluorophenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;
- 2-(pyridin-2-yl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;
- 2-(4-ethylphenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;
- 2-(2,4-difluorophenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;
- 2-(3,4-dimethylphenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;
- 20 2-(3-methylphenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;
- 2-(3-fluorophenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;
- 2-(4-isopropylphenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;
- 2-(4-ethoxyphenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;
- 2-(4-chlorophenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;
- 25 2-(4-methoxyphenyl)-2,5,6,7,8,9,10-heptahydrocyclohepta[c]pyrazolo[4,3-c]pyridazin-3-one;
- 2-(4-methylphenyl)-2,5,6,7,8,9,10-heptahydrocyclohepta[c]pyrazolo[4,3-c]pyridazin-3-one;
- 2-(4-chlorophenyl)-2,5,6,7,8,9,10-heptahydrocyclohepta[c]pyrazolo[4,3-c]pyridazin-3-one;
- 30 c]pyridazin-3-one;

2-(4-fluorophenyl)-2,5,6,7,8,9,10-heptahydrocyclohepta[c]pyrazolo[4,3-c]pyridazin-3-one;

2-(3-methoxyphenyl)-2,5,6,7,8,9,10-heptahydrocyclohepta[c]pyrazolo[4,3-c]pyridazin-3-one;

5 2-(pyridin-2-yl)-2,5,6,7,8,9,10-heptahydrocyclohepta[c]pyrazolo[4,3-c]pyridazin-3-one;

2-(4-methylpyridin-2-yl)-2,5,6,7,8,9,10-heptahydrocyclohepta[c]pyrazolo-[4,3-c]pyridazin-3-one;

and salts and prodrugs thereof.

10 Also provided by the present invention is a method for the treatment and/or prevention of anxiety which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined above or a pharmaceutically acceptable salt thereof.

Further provided by the present invention is a method for the  
15 treatment and/or prevention of convulsions (e.g. in a patient suffering from epilepsy or a related disorder) which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined above or a pharmaceutically acceptable salt thereof.

The binding affinity ( $K_i$ ) of the compounds according to the present  
20 invention for the  $\alpha 3$  subunit of the human GABA<sub>A</sub> receptor is conveniently as measured in the assay described hereinbelow. The  $\alpha 3$  subunit binding affinity ( $K_i$ ) of the compounds of the invention is ideally 10 nM or less, preferably 2 nM or less, and more preferably 1 nM or less.

The compounds according to the present invention will ideally elicit  
25 at least a 40%, preferably at least a 50%, and more preferably at least a 60%, potentiation of the GABA EC<sub>20</sub> response in stably transfected recombinant cell lines expressing the  $\alpha 3$  subunit of the human GABA<sub>A</sub> receptor. Moreover, the compounds of the invention will ideally elicit at most a 30%, preferably at most a 20%, and more preferably at most a 10%,  
30 potentiation of the GABA EC<sub>20</sub> response in stably transfected recombinant cell lines expressing the  $\alpha 1$  subunit of the human GABA<sub>A</sub> receptor.

The potentiation of the GABA EC<sub>20</sub> response in stably transfected cell lines expressing the  $\alpha 3$  and  $\alpha 1$  subunits of the human GABA<sub>A</sub> receptor can conveniently be measured by procedures analogous to the protocol described in Wafford *et al.*, *Mol. Pharmacol.*, 1996, 50, 670-678. The  
5 procedure will suitably be carried out utilising cultures of stably transfected eukaryotic cells, typically of stably transfected mouse Ltk-fibroblast cells.

The compounds according to the present invention exhibit anxiolytic activity, as may be demonstrated by a positive response in the  
10 elevated plus maze and conditioned suppression of drinking tests (cf. Dawson *et al.*, *Psychopharmacology*, 1995, 121, 109-117). Moreover, the compounds of the invention are substantially non-sedating, as may be confirmed by an appropriate result obtained from the response sensitivity (chain-pulling) test (cf. Bayley *et al.*, *J. Psychopharmacol.*, 1996, 10, 206-  
15 213).

The compounds according to the present invention may also exhibit anticonvulsant activity. This can be demonstrated by the ability to block pentylenetetrazole-induced seizures in rats and mice, following a protocol analogous to that described by Bristow *et al.* in *J. Pharmacol. Exp. Ther.*,  
20 1996, 279, 492-501.

In order to elicit their behavioural effects, the compounds of the invention will ideally be brain-penetrant; in other words, these compounds will be capable of crossing the so-called "blood-brain barrier". Preferably, the compounds of the invention will be capable of exerting their beneficial  
25 therapeutic action following administration by the oral route.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules,  
30 sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral,

parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil

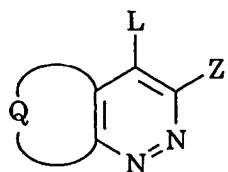
suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as

5 tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

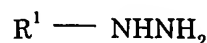
In the treatment of anxiety, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be

10 administered on a regimen of 1 to 4 times per day.

The compounds in accordance with the present invention may be prepared by a process which comprises reacting a compound of formula III with a hydrazine derivative of formula IV, or an acid addition salt thereof:



(III)



(IV)

15

wherein Q and R<sup>1</sup> are as defined above, L represents a readily displaceable group, and Z represents a reactive carboxylate moiety.

The acid addition salt of the hydrazine derivative of formula IV is

20 suitably a mineral acid addition salt, typically the hydrochloride salt.

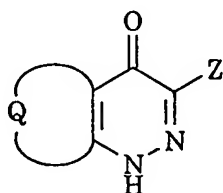
The readily displaceable group L in the compound of formula III is suitably a halogen atom, e.g. chloro.

Suitable values for the reactive carboxylate moiety Z include esters, for example C<sub>1-4</sub> alkyl esters; acid anhydrides, including mixed anhydrides

25 with C<sub>1-4</sub> alkanolic acids; acid halides, for example acid chlorides; and acylimidazoles. Suitably, Z represents ethoxycarbonyl.

The reaction between compounds III and IV may conveniently be carried out under basic conditions in a suitable solvent, e.g. sodium carbonate or *N,N*-diisopropylethylamine (Hünig's base) in xylene.

- 5 A typical intermediate of formula III wherein the readily displaceable group L is chloro may conveniently be prepared by treating the compound of formula V:

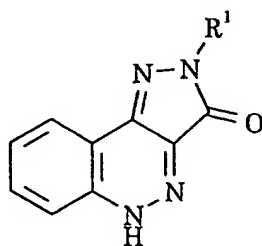


(V)

- 10 wherein Q and Z are as defined above; with *p*-toluenesulphonyl chloride, advantageously in the presence of lithium chloride and pyridine.

The reaction is conveniently effected in an inert solvent such as dichloromethane, typically at the reflux temperature of the solvent.

- 15 In an alternative procedure, the compounds according to the invention wherein Q represents  $-(CH_2)_4-$  may be prepared by a process which comprises reducing a compound of formula VI:



(VI)

- 20 wherein R<sup>1</sup> is as defined above.

The reaction is conveniently brought about by treating the compound of formula VI with hydrogen in the presence of a hydrogenation



catalyst such as platinum oxide, or palladium on charcoal, typically in the presence of trifluoroacetic acid.

The intermediates of formula VI above may be prepared by methods analogous to those described in US-4591589 and GB-A-2166439.

5       Where they are not commercially available, the starting materials of formula IV and V may be prepared by methods analogous to those described in the accompanying Examples, or by standard methods well known from the art.

10       It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art.

15       Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by  
20       standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-*p*-toluoyl-*d*-tartaric acid and/or (+)-di-*p*-toluoyl-*l*-tartaric acid, followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric  
25       esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

30       During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene &

P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

5 The following Examples illustrate the preparation of compounds according to the invention.

The compounds in accordance with this invention potently inhibit the binding of [<sup>3</sup>H]-flumazenil to the benzodiazepine binding site of human GABA<sub>A</sub> receptors containing the  $\alpha 2$  or  $\alpha 3$  subunit stably expressed in Ltk-cells.

10

#### *Reagents*

- Phosphate buffered saline (PBS).
- Assay buffer: 10 mM KH<sub>2</sub>PO<sub>4</sub>, 100 mM KCl, pH 7.4 at room temperature.
- 15 • [<sup>3</sup>H]-Flumazenil (18 nM for  $\alpha 1\beta 3\gamma 2$  cells; 18 nM for  $\alpha 2\beta 3\gamma 2$  cells; 10 nM for  $\alpha 3\beta 3\gamma 2$  cells) in assay buffer.
- Flunitrazepam 100  $\mu$ M in assay buffer.
- Cells resuspended in assay buffer (1 tray to 10 ml).

#### 20 *Harvesting Cells*

Supernatant is removed from cells. PBS (approximately 20 ml) is added. The cells are scraped and placed in a 50 ml centrifuge tube. The procedure is repeated with a further 10 ml of PBS to ensure that most of the cells are removed. The cells are pelleted by centrifuging for 20 min at  
25 3000 rpm in a benchtop centrifuge, and then frozen if desired. The pellets are resuspended in 10 ml of buffer per tray (25 cm x 25 cm) of cells.

#### *Assay*

Can be carried out in deep 96-well plates or in tubes. Each tube  
30 contains:

- 300  $\mu$ l of assay buffer.
  - 50  $\mu$ l of [ $^3$ H]-flumazenil (final concentration for  $\alpha 1\beta 3\gamma 2$ : 1.8 nM; for  $\alpha 2\beta 3\gamma 2$ : 1.8 nM; for  $\alpha 3\beta 3\gamma 2$ : 1.0 nM).
  - 50  $\mu$ l of buffer or solvent carrier (e.g. 10% DMSO) if compounds are
- 5 dissolved in 10% DMSO (total); test compound or flunitrazepam (to determine non-specific binding), 10  $\mu$ M final concentration.
- 100  $\mu$ l of cells.

Assays are incubated for 1 hour at 40°C, then filtered using either a Tomtec or Brandel cell harvester onto GF/B filters followed by 3 x 3 ml

10 washes with ice cold assay buffer. Filters are dried and counted by liquid scintillation counting. Expected values for total binding are 3000-4000 dpm for total counts and less than 200 dpm for non-specific binding if using liquid scintillation counting, or 1500-2000 dpm for total counts and less than 200 dpm for non-specific binding if counting with meltilex solid

15 scintillant. Binding parameters are determined by non-linear least squares regression analysis, from which the inhibition constant  $K_i$  can be calculated for each test compound.

The compounds of the accompanying Examples were tested in the above assay, and all were found to possess a  $K_i$  value for displacement of

20 [ $^3$ H]-flumazenil from the  $\alpha 2$  and/or  $\alpha 3$  subunit of the human GABA<sub>A</sub> receptor of 100 nM or less.

### EXAMPLE 1

25 2-(4-Methoxyphenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one

4-Oxo-1,4,5,6,7,8-hexahydrocinnoline-3-carboxylic acid ethyl ester

To 4-oxo-1,4-dihydrocinnoline-3-carboxylic acid ethyl ester (4.5 g) dissolved in trifluoroacetic acid (20 ml) was added platinum oxide (0.2 g).

30 The reaction mixture was hydrogenated at 50 psi until no further uptake of hydrogen was observed. The catalyst was collected by filtration, the

filtrate was poured onto ice, the pH was raised to pH6 with base, the resulting precipitate was collected by filtration, washed with water and dried to give a solid (2.8 g, 61%).  $\delta_H$  (250MHz; DMSO- $d_6$ ) 1.26 (3H, t, J=7Hz, CH<sub>3</sub>), 1.68 (4H, m, CH<sub>2</sub>), 2.33 (2H, t, J=5.5Hz, CH<sub>2</sub>), 2.62 (2H, t, J=5.5Hz, CH<sub>2</sub>), 4.25 (2H, t, J=7Hz, CH<sub>2</sub>), 13.19 (1H, br s, NH), m/z (ESP+) 223 (MH<sup>+</sup>).

4-Chloro-5,6,7,8-tetrahydrocinnoline-3-carboxylic acid ethyl ester

To a slurry of 4-oxo-1,4,5,6,7,8-hexahydrocinnoline-3-carboxylic acid ethyl ester (1 g), lithium chloride (0.19 g) and pyridine (0.36 ml) in dichloromethane (30 ml) was added *p*-toluenesulphonyl chloride (0.85 g). The reaction mixture was heated at reflux for 20 h. The solid was collected by filtration, and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography using a gradient elution: CH<sub>2</sub>Cl<sub>2</sub> (500 ml), CH<sub>2</sub>Cl<sub>2</sub>/MeOH 99:1 (500 ml), CH<sub>2</sub>Cl<sub>2</sub>/MeOH 98:2 (1 litre). The appropriate fractions were combined and evaporated under reduced pressure to give a solid (0.65g, 61%).  $\delta_H$  (360MHz; CDCl<sub>3</sub>) 1.44 (3H, t, J=7Hz, CH<sub>3</sub>), 1.89 (4H, m, CH<sub>2</sub>), 2.85 (2H, t, J=5.7Hz, CH<sub>2</sub>), 2.62 (2H, t, J=5.7Hz, CH<sub>2</sub>), 4.51 (2H, t, J=7Hz, CH<sub>2</sub>), m/z (ESP+) 241/243 (MH<sup>+</sup>).

2-(4-Methoxyphenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-*c*]cinnolin-3-one

4-Chloro-5,6,7,8-tetrahydrocinnoline-3-carboxylic acid ethyl ester (0.5 g), 4-methoxyphenylhydrazine hydrochloride (0.37 g) and potassium carbonate (0.29 g) in xylene were heated under reflux for 3 h. The solid was collected by filtration, washed with hexane, then water. The residue was absorbed onto silica and purified by flash chromatography using a gradient elution: CH<sub>2</sub>Cl<sub>2</sub> (250 ml), CH<sub>2</sub>Cl<sub>2</sub>/(MeOH/NH<sub>3</sub> 10:1) 99:1 (250 ml), CH<sub>2</sub>Cl<sub>2</sub>/(MeOH/NH<sub>3</sub> 10:1) 98:2 (250 ml), CH<sub>2</sub>Cl<sub>2</sub>/(MeOH/NH<sub>3</sub> 10:1) 97:3 (250 ml), CH<sub>2</sub>Cl<sub>2</sub>/(MeOH/NH<sub>3</sub> 10:1) 96:4 (250 ml), CH<sub>2</sub>Cl<sub>2</sub>/(MeOH/NH<sub>3</sub> 10:1) 95:5 (250 ml). The appropriate fractions were combined and

evaporated under reduced pressure to give a solid (79 mg, 13%).  $\delta_H$  (360MHz; DMSO) 1.83 (4H, m, CH<sub>2</sub>), 2.67 (2H, t, J=5.3Hz, CH<sub>2</sub>), 2.72 (2H, t, J=5.3Hz, CH<sub>2</sub>), 3.78 (3H, s, OCH<sub>3</sub>), 7.02 (2H, d, J=9Hz, ArH), 8.06 (2H, d, J=9Hz, CH<sub>2</sub>), m/z (ESP+) 297 (MH<sup>+</sup>).

5

## EXAMPLE 2

### 2-(4-Fluorophenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one

4-Chloro-5,6,7,8-tetrahydrocinnoline-3-carboxylic acid ethyl ester  
10 (0.5 g), 4-fluorophenylhydrazine hydrochloride (0.34 g) and Hünig's base (0.73 ml) in xylene under nitrogen were heated under reflux for 2 h. The solid was collected by filtration, washed with diethyl ether, water and diethyl ether. The residue was recrystallised from ethanol to give the title compound (136 mg, 13%).  $\delta_H$  (360MHz; DMSO-d<sub>6</sub>) 1.83 (4H, m, CH<sub>2</sub>), 2.67  
15 (2H, t, J=5.3Hz, CH<sub>2</sub>), 2.72 (2H, t, J=5.3Hz, CH<sub>2</sub>), 3.78 (3H, s, OCH<sub>3</sub>), 7.02 (2H, d, J=9Hz, ArH), 8.06 (2H, d, J=9Hz, ArH), m/z (ESP+) 285 (MH<sup>+</sup>). C<sub>15</sub>H<sub>13</sub>FN<sub>4</sub>O requires C, 63.37; H, 4.61; N, 19.71; found C, 62.96; H, 4.36; N, 19.48%.

20

## EXAMPLE 3

### 2-(4-Methylphenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one

Using the procedure outlined in Example 2 the title compound was made.  $\delta_H$  (360MHz; DMSO-d<sub>6</sub>) 1.83 (4H, m, CH<sub>2</sub>), 2.33 (3H, s, CH<sub>3</sub>), 2.67  
25 (2H, t, J=5.5Hz, CH<sub>2</sub>), 2.75 (2H, t, J=5.3Hz, CH<sub>2</sub>), 7.26 (2H, d, J=9Hz, ArH), 8.07 (2H, d, J=9Hz, ArH), m/z (ESP+) 281 (MH<sup>+</sup>). C<sub>16</sub>H<sub>16</sub>N<sub>4</sub>O requires C, 68.55; H, 5.75; N, 19.99; found C, 68.60; H, 5.47; N, 19.89%.

**EXAMPLE 4****2-(3-Chlorophenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one**

Using the procedure outlined in Example 2 the title compound was  
5 made.  $\delta_H$  (360MHz; DMSO- $d_6$ ) 1.83 (4H, m, CH<sub>2</sub>), 2.67 (2H, t, J=5.8Hz, CH<sub>2</sub>), 2.73 (2H, t, J=5.8Hz, CH<sub>2</sub>), 7.27 (1H, d, J=8Hz, ArH), 7.48 (1H, t, J=8Hz, ArH), 8.07 (1H, d, J=8Hz, ArH), 8.17 (1H, t, J=8Hz, ArH), m/z (ESP+) 300/302 (MH<sup>+</sup>). C<sub>15</sub>H<sub>13</sub>ClN<sub>4</sub>O requires C, 59.90; H, 4.36; N, 18.63; found C, 59.82; H, 4.51; N, 18.11%.

10

**EXAMPLE 5****2-(2-Fluorophenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one**

4-Chloro-5,6,7,8-tetrahydrocinnoline-3-carboxylic acid ethyl ester  
15 (0.5 g), 2-fluorophenylhydrazine hydrochloride (0.34 g) and Hünig's base (0.73 ml) in xylene were heated under reflux for 3 h. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography using a gradient elution: CH<sub>2</sub>Cl<sub>2</sub> (500 ml), CH<sub>2</sub>Cl<sub>2</sub>/(MeOH/NH<sub>3</sub> 10:1) 99:1 (500 ml), CH<sub>2</sub>Cl<sub>2</sub>/(MeOH/NH<sub>3</sub> 10:1) 98:2  
20 (500 ml), CH<sub>2</sub>Cl<sub>2</sub>/(MeOH/NH<sub>3</sub> 10:1) 97:3 (500 ml), CH<sub>2</sub>Cl<sub>2</sub>/(MeOH/NH<sub>3</sub> 10:1) 96:4 (500 ml), CH<sub>2</sub>Cl<sub>2</sub>/(MeOH/NH<sub>3</sub> 10:1) 95:5 (500ml). The appropriate fractions were combined and evaporated under reduced pressure to give a solid (250 mg, 42%).  $\delta_H$  (360MHz; DMSO) 1.83 (4H, m, CH<sub>2</sub>), 2.61 (2H, t, J=5.3Hz, CH<sub>2</sub>), 2.75 (2H, t, J=5.3Hz, CH<sub>2</sub>), 7.30-7.57  
25 (4H, m, ArH), m/z (ESP+) 285 (MH<sup>+</sup>). C<sub>15</sub>H<sub>13</sub>FN<sub>4</sub>O requires C, 63.37; H, 4.61; N, 19.71; found C, 63.18; H, 4.70; N, 19.35%.

**EXAMPLE 6****2-(Pyridin-2-yl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one**

Using the procedure outlined in Example 2 the title compound was  
5 made.  $\delta_H$  (360MHz; DMSO- $d_6$ ) 1.84 (4H, m, CH<sub>2</sub>), 2.65 (2H, t, J=5.8Hz, CH<sub>2</sub>), 2.74 (2H, t, J=5.8Hz, CH<sub>2</sub>), 7.28 (1H, t, J=7Hz, ArH), 7.89 (1H, t, J=7Hz, ArH), 8.14 (1H, d, J=7Hz, ArH), 8.50 (1H, d, J=7Hz, ArH), m/z (ESP+) 268 (MH<sup>+</sup>).

10

**EXAMPLE 7****2-(4-Ethylphenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one**

Using the procedure outlined in Example 2 the title compound was  
made.  $\delta_H$  (360MHz; DMSO- $d_6$ ) 1.20 (3H, t, J=7.5Hz, CH<sub>3</sub>), 1.83 (4H, m, CH<sub>2</sub>), 2.51 (2H, q, J=7.5Hz, CH<sub>2</sub>), 2.66 (2H, t, J=5.8Hz, CH<sub>2</sub>), 2.73 (2H, t, J=5.8Hz, CH<sub>2</sub>), 7.28 (1H, d, J=8.5Hz, ArH), 8.08 (1H, d, J=8.5Hz, ArH), m/z (ESP+) 295 (MH<sup>+</sup>).

20

**EXAMPLE 8****2-(2,4-Difluorophenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one**

Using the procedure outlined in Example 5 the title compound was  
made.  $\delta_H$  (360MHz; DMSO- $d_6$ ) 1.82 (4H, m, CH<sub>2</sub>), 2.60 (2H, t, J=5.8Hz, CH<sub>2</sub>), 2.75 (2H, t, J=5.8Hz, CH<sub>2</sub>), 7.22 (1H, t, J=9Hz, ArH), 7.46 (1H, t, J=9Hz, ArH), 7.60 (1H, t, J=9Hz, ArH), m/z (ESP+) 303 (MH<sup>+</sup>).

25

**EXAMPLE 9****2-(3,4-Dimethylphenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one**

Using the procedure outlined in Example 5 the title compound was  
made.  $\delta_H$  (360MHz; DMSO- $d_6$ ) 1.83 (4H, m, CH<sub>2</sub>), 2.24 (3H, s, CH<sub>3</sub>), 2.28

30

(3H, s, CH<sub>3</sub>), 2.67 (2H, t, J=5.8Hz, CH<sub>2</sub>), 2.75 (2H, t, J=5.8Hz, CH<sub>2</sub>), 7.19 (1H, d, J=8Hz, ArH), 7.90 (1H, d, J=8Hz, ArH), 7.95 (1H, s, ArH), m/z (ESP+) 295 (MH<sup>+</sup>).

5

**EXAMPLE 10****2-(3-Methylphenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one**

Using the procedure outlined in Example 5 the title compound was made.  $\delta_H$  (360MHz; DMSO-d<sub>6</sub>) 1.83 (4H, m, CH<sub>2</sub>), 2.37 (3H, s, CH<sub>3</sub>), 2.67 (2H, t, J=5.8Hz, CH<sub>2</sub>), 2.73 (2H, t, J=5.8Hz, CH<sub>2</sub>), 7.02 (H, d, J=7Hz, ArH), 7.32 (1H, t, J=7Hz, ArH), 7.99 (1H, s, ArH), 8.00 (1H, d, J=7Hz, ArH), m/z (ESP+) 281 (MH<sup>+</sup>).

15

**EXAMPLE 11****2-(3-Fluorophenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one**

Using the procedure outlined in Example 5 the title compound was made.  $\delta_H$  (360MHz; DMSO-d<sub>6</sub>) 1.83 (4H, m, CH<sub>2</sub>), 2.67 (2H, t, J=5.8Hz, CH<sub>2</sub>), 2.73 (2H, t, J=5.8Hz, CH<sub>2</sub>), 7.04 (1H, m, ArH), 7.50 (1H, m, ArH), 8.04 (2H, m, ArH), m/z (ESP+) 285 (MH<sup>+</sup>).

20

**EXAMPLE 12****2-(4-Isopropylphenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one**

Using the procedure outlined in Example 5 the title compound was made.  $\delta_H$  (360MHz; DMSO-d<sub>6</sub>) 1.21 (3H, s, CH<sub>3</sub>), 1.23 (3H, s, CH<sub>3</sub>), 1.83 (4H, m, CH<sub>2</sub>), 2.67 (2H, t, J=5.8Hz, CH<sub>2</sub>), 2.73 (2H, t, J=5.8Hz, CH<sub>2</sub>), 2.73 (1H, m, CH), 7.31 (2H, d, J=8.6Hz, ArH), 8.06 (2H, d, J=8.6Hz, ArH), m/z (ESP+) 309 (MH<sup>+</sup>).

30



**EXAMPLE 13****2-(4-Ethoxyphenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one**

Using the procedure outlined in Example 5 the title compound was  
5 made.  $\delta_H$  (360MHz; DMSO- $d_6$ ) 1.34 (3H, t, J=7Hz, CH<sub>3</sub>), 1.83 (4H, m, CH<sub>2</sub>), 2.67 (2H, t, J=5.8Hz, CH<sub>2</sub>), 2.74 (2H, t, J=5.8Hz, CH<sub>2</sub>), 2.73 (H, m, CH), 7.31 (2H, d, J=8.6Hz, ArH), 8.06 (2H, d, J=8.6Hz, ArH), m/z (ESP+) 309 (MH<sup>+</sup>).

10

**EXAMPLE 14****2-(4-Chlorophenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one****2-(4-Chlorophenyl)-2,5-dihydropyrazolo[4,3-c]cinnolin-3-one**

15

Prepared as described in US Patent No. 4,591,589.

**2-(4-Chlorophenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one**

20

To 2-(4-chlorophenyl)-2,5-dihydropyrazolo[4,3-c]cinnolin-3-one (0.5 g) dissolved in trifluoroacetic acid (20 ml) was added platinum oxide (0.2 g). The reaction mixture was hydrogenated at 50 psi until no further uptake of hydrogen was observed. The catalyst was collected by filtration, the filtrate was poured onto ice and basified with ammonia. On the addition of dichloromethane a solid precipitated out; the solid was collected by filtration, washed with water and dried. Recrystallisation  
25 from ethanol gave the title compound.  $\delta_H$  (360MHz; DMSO- $d_6$ ) 1.83 (4H, m, CH<sub>2</sub>), 2.67 (2H, t, J=5.7Hz, CH<sub>2</sub>), 2.75 (2H, t, J=5.7Hz, CH<sub>2</sub>), 7.51 (2H, d, J=9Hz, ArH), 8.23 (2H, d, J=9Hz, ArH), m/z (ESP+) 301/303 (MH<sup>+</sup>).

EXAMPLE 152-(4-Methoxyphenyl)-2,5,6,7,8,9,10-heptahydrocyclohepta[c]pyrazolo[4,3-c]pyridazin-3-one

5

3-(2-Chlorocyclohept-1-enyl)-2-diazo-3-oxopropionic acid ethyl ester

To a solution of 2-chlorocyclohept-1-enecarbonyl chloride (4.6 g) and ethyl diazoacetate (2.8 ml) in THF (30 ml) cooled to -70C was added a solution of lithium 2,2,6,6-tetramethylpiperidine (1 equiv.) dropwise. On completion of the addition the reaction mixture was stirred for 1 h. The reaction mixture was quenched by pouring into 1M citric acid (100 ml), then extracted with ether (3 x 200 ml). The ether extracts were combined, washed with brine, dried over magnesium sulphate, filtered and evaporated under reduced pressure to give an oil. The oil was purified by flash chromatography using a gradient elution: hexane/ether (10:1) 500 ml, hexane/ether (9:1) 500 ml, hexane/ether (8:2) 500 ml. The appropriate fractions were combined and evaporated under reduced pressure to give a yellow oil.  $\delta_H$  (360MHz;  $CDCl_3$ ) 1.33 (3H, t,  $J=7$ Hz,  $CH_3$ ), 1.74 (6H, m,  $CH_2$ ), 2.32 (2H, m,  $CH_2$ ), 2.64 (2H, m,  $CH_2$ ), 4.29 (2H, t,  $J=7$ Hz,  $CH_2$ ).

15  
204-Oxo-4,5,6,7,8,9-hexahydro-1H-cyclohepta[c]pyridazine-3-carboxylic acid ethyl ester

To a solution of 3-(2-chlorocyclohept-1-enyl)-2-diazo-3-oxopropionic acid ethyl ester (1 g) in 1,4-dioxan (20 ml) was added a solution of tri-*n*-butylphosphine (1 ml) in 1,4-dioxan (10 ml). On completion of the addition the reaction mixture was stirred at room temperature for 30 minutes then heated to reflux for 2 h. The solvent was evaporated under reduced pressure and the residue purified by chromatography using a gradient elution:  $CH_2Cl_2$  (250 ml),  $CH_2Cl_2$ /MeOH 99:1 (250 ml),  $CH_2Cl_2$ /MeOH 98:2 (250 ml),  $CH_2Cl_2$ /MeOH 97:3 (250 ml),  $CH_2Cl_2$ /MeOH 96:4 (250 ml). The appropriate fractions were combined and evaporated under reduced

25  
30

pressure to give a solid (360 mg, 41%).  $C_{12}H_{16}N_2O_3$  requires C, 61.00; H, 6.83; N, 11.86. Found C, 60.80; H, 6.88; N, 11.84%.  $\delta_H$  (250MHz;  $CDCl_3$ ) 1.42 (3H, t,  $J=7$ Hz,  $CH_3$ ), 1.62 (2H, m,  $CH_2$ ), 1.73 (2H, m,  $CH_2$ ), 1.87 (2H, m,  $CH_2$ ), 2.86 (2H, m,  $CH_2$ ), 3.09 (2H, m,  $CH_2$ ), 4.48 (2H, t,  $J=7$ Hz,  $CH_2$ ),  
5 m/z (ESP+) 237 ( $MH^+$ ).

4-Chloro-6,7,8,9-tetrahydro-5H-cyclohepta[c]pyridazine-3-carboxylic acid ethyl ester

To a solution of 4-oxo-4,5,6,7,8,9-hexahydro-1H-cyclohepta[c]pyridazine-3-carboxylic acid ethyl ester (2.7 g) and pyridine (0.93 ml) in dichloromethane (150 ml) was added *p*-toluenesulphonyl chloride (2.2 g). The reaction mixture was heated at reflux for 20 h. The reaction mixture was washed with 1M potassium carbonate solution, brine, dried over magnesium sulphate, filtered and evaporated under  
15 reduced pressure to give an oil. The oil was purified by flash chromatography using a gradient elution:  $CH_2Cl_2$  (500 ml),  $CH_2Cl_2/MeOH$  99:1 (500 ml),  $CH_2Cl_2/MeOH$  98:2 (500 ml),  $CH_2Cl_2/MeOH$  97:3 (500 ml),  $CH_2Cl_2/MeOH$  96:4 (500 ml). The appropriate fractions were combined and evaporated under reduced pressure to give a solid (0.65 g, 22%).  
20  $C_{12}H_{15}ClN_2O_2$  requires C, 56.58; H, 5.93; N, 11.00. Found C, 56.52; H, 6.06; N, 11.01%.  $\delta_H$  (360MHz;  $CDCl_3$ ) 1.44 (3H, t,  $J=7$ Hz,  $CH_3$ ), 1.70 (2H, m,  $CH_2$ ), 1.77 (2H, m,  $CH_2$ ), 1.92 (2H, m,  $CH_2$ ), 3.06 (2H, m,  $CH_2$ ), 3.32 (2H, m,  $CH_2$ ), 4.51 (2H, t,  $J=7$ Hz,  $CH_2$ ), m/z (ESP+) 255/257 ( $MH^+$ ).

25 2-(4-Methoxyphenyl)-2,5,6,7,8,9,10-heptahydrocyclohepta[c]pyrazolo[4,3-c]pyridazin-3-one

4-Chloro-6,7,8,9-tetrahydro-5H-cyclohepta[c]pyridazine-3-carboxylic acid ethyl ester (0.25 g), 4-methoxyphenylhydrazine hydrochloride (0.17 g) and Hünig's base (0.34 ml) in xylene (10 ml) were heated under reflux for  
30 4 h. The solid was collected by filtration, washed with hexane and dried. The solid was partitioned between dichloromethane and water, the

dichloromethane extracts were combined, dried over magnesium sulphate, filtered and evaporated under reduced pressure to give a solid.  $\delta_H$  (360MHz; DMSO- $d_6$ ) 1.66 (4H, m, CH<sub>2</sub>), 1.86 (2H, m, CH<sub>2</sub>), 2.88 (2H, m, CH<sub>2</sub>), 2.93 (2H, m, CH<sub>2</sub>), 3.78 (3H, s, OCH<sub>3</sub>), 7.02 (2H, d, J=9Hz, ArH),  
5 8.10 (2H, d, J=9Hz, ArH), m/z (ESP+) 311 (MH<sup>+</sup>).

### EXAMPLE 16

#### 10 2-(4-Methylphenyl)-2,5,6,7,8,9,10-heptahydrocyclohepta[c]pyrazolo[4,3-c]pyridazin-3-one

4-Chloro-6,7,8,9-tetrahydro-5*H*-cyclohepta[c]pyridazine-3-carboxylic acid ethyl ester (0.25 g), 4-methylphenylhydrazine hydrochloride (0.17 g) and Hünig's base (0.34 ml) in xylene (10 ml) were heated under reflux for 5 h. The solvent was evaporated under reduced pressure. The residue  
15 was partitioned between ethyl acetate and water, the solid which precipitated out was collected by filtration, washed with water, then ether and dried.  $\delta_H$  (360MHz; DMSO- $d_6$ ) 1.66 (4H, m, CH<sub>2</sub>), 1.86 (2H, m, CH<sub>2</sub>), 2.33 (2H, s, CH<sub>3</sub>), 2.88 (2H, m, CH<sub>2</sub>), 2.94 (2H, m, CH<sub>2</sub>), 7.25 (2H, d, J=9Hz, ArH), 8.10 (2H, d, J=9Hz, ArH), m/z (ESP+) 295 (MH<sup>+</sup>).

20

### EXAMPLE 17

#### 25 2-(4-Chlorophenyl)-2,5,6,7,8,9,10-heptahydrocyclohepta[c]pyrazolo[4,3-c]pyridazin-3-one

4-Chloro-6,7,8,9-tetrahydro-5*H*-cyclohepta[c]pyridazine-3-carboxylic acid ethyl ester (0.25 g), 4-chlorophenylhydrazine hydrochloride (0.18 g) and Hünig's base (0.34 ml) in xylene (10 ml) were heated under reflux for 3 h. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography using a gradient elution: CH<sub>2</sub>Cl<sub>2</sub> (250  
30 ml), CH<sub>2</sub>Cl<sub>2</sub>/MeOH 99:1 (250 ml), CH<sub>2</sub>Cl<sub>2</sub>/MeOH 98:2 (250 ml), CH<sub>2</sub>Cl<sub>2</sub>/MeOH 97:3 (250 ml), CH<sub>2</sub>Cl<sub>2</sub>/MeOH 96:4 (250 ml). The

appropriate fractions were combined and evaporated under reduced pressure to give a solid (53 mg, 17%).  $\delta_H$  (360MHz; DMSO- $d_6$ ) 1.66 (4H, m, CH<sub>2</sub>), 1.86 (2H, m, CH<sub>2</sub>), 2.88 (2H, m, CH<sub>2</sub>), 2.94 (2H, m, CH<sub>2</sub>), 7.51 (2H, d, J=9Hz, ArH), 8.27 (2H, d, J=9Hz, ArH), m/z (ESP+) 315 (MH<sup>+</sup>).

- 5 C<sub>16</sub>H<sub>15</sub>ClN<sub>4</sub>O requires C, 61.05; H, 4.80; N, 17.80. Found C, 60.75; H, 4.54; N, 17.54%.

### EXAMPLE 18

- 10 2-(4-Fluorophenyl)-2,5,6,7,8,9,10-heptahydrocyclohepta[c]pyrazolo[4,3-c]pyridazin-3-one

Using the procedure as shown in Example 17 the title compound was obtained.  $\delta_H$  (360MHz; DMSO- $d_6$ ) 1.66 (4H, m, CH<sub>2</sub>), 1.86 (2H, m, CH<sub>2</sub>), 2.88 (2H, m, CH<sub>2</sub>), 2.94 (2H, m, CH<sub>2</sub>), 7.29 (2H, t, J=9Hz, ArH), 8.24  
15 (2H, m, ArH), m/z (ESP+) 299 (MH<sup>+</sup>).

### EXAMPLE 19

- 20 2-(3-Methoxyphenyl)-2,5,6,7,8,9,10-heptahydrocyclohepta[c]pyrazolo[4,3-c]pyridazin-3-one

Using the procedure as shown in Example 17 the title compound was obtained.  $\delta_H$  (360MHz; DMSO- $d_6$ ) 1.66 (4H, m, CH<sub>2</sub>), 1.86 (2H, m, CH<sub>2</sub>), 2.88 (2H, m, CH<sub>2</sub>), 2.92 (2H, m, CH<sub>2</sub>), 3.80 (3H, s, OCH<sub>3</sub>), 6.79 (1H, d, J=8Hz, ArH), 7.35 (1H, t, J=8Hz, ArH), 7.82 (1H, d, J=8Hz, ArH), 8.87  
25 (1H, s, ArH), m/z (ESP+) 311 (MH<sup>+</sup>). C<sub>17</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub> requires C, 65.79; H, 5.85; N, 18.05. Found C, 66.07; H, 5.73; N, 17.77%.

**EXAMPLE 20****2-(Pyridin-2-yl)-2,5,6,7,8,9,10-heptahydrocyclohepta[c]pyrazolo[4,3-c]pyridazin-3-one**

5        Using the procedure as shown in Example 17 the title compound was obtained.  $\delta_H$  (360MHz; DMSO- $d_6$ ) 1.66 (4H, m, CH<sub>2</sub>), 1.86 (2H, m, CH<sub>2</sub>), 2.88 (2H, m, CH<sub>2</sub>), 2.93 (2H, m, CH<sub>2</sub>), 7.28 (1H, m, ArH), 7.90 (1H, t, J=8Hz, ArH), 8.16 (1H, d, J=8Hz, ArH), 8.54 (1H, d, J=8Hz, ArH), m/z (ESP+) 282 (MH<sup>+</sup>).

10

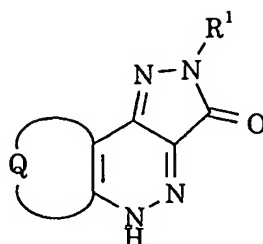
**EXAMPLE 21****2-(4-Methylpyridin-2-yl)-2,5,6,7,8,9,10-heptahydrocyclohepta[c]pyrazolo[4,3-c]pyridazin-3-one**

15        Using the procedure as shown in Example 17 the title compound was obtained.  $\delta_H$  (360MHz; DMSO- $d_6$ ) 1.65 (4H, m, CH<sub>2</sub>), 1.86 (2H, m, CH<sub>2</sub>), 2.33 (3H, s, CH<sub>3</sub>), 2.87 (2H, m, CH<sub>2</sub>), 2.93 (2H, m, CH<sub>2</sub>), 7.73 (1H, d, J=8Hz, ArH), 8.04 (1H, d, J=8Hz, ArH), 8.34 (1H, s, ArH), m/z (ESP+) 296 (MH<sup>+</sup>). C<sub>16</sub>H<sub>17</sub>N<sub>5</sub>O requires C, 65.07; H, 5.80; N 23.71. Found C, 65.10; H, 5.75; N, 23.49%.

20

CLAIMS:

1. A compound of formula I, or a salt or prodrug thereof:



(I)

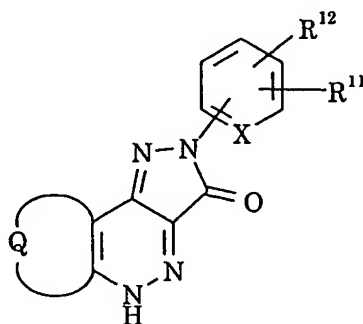
wherein

Q represents  $-(CH_2)_n-$ ;

n is 3, 4, 5 or 6; and

R¹ represents aryl or heteroaryl, either of which groups may be optionally substituted.

2. A compound as claimed in claim 1 represented by formula II, and salts and prodrugs thereof:



(II)

wherein

Q is as defined in claim 1;

X represents CH or nitrogen; and

R<sup>11</sup> and R<sup>12</sup> independently represent hydrogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylsulphonyl, C<sub>2-6</sub> alkylcarbonyl, halogen, cyano or trifluoromethyl.

5           3.     A compound as claimed in claim 1 or claim 2 wherein Q represents -(CH<sub>2</sub>)<sub>n</sub>- in which n is 4 or 5.

          4.     A compound as claimed in claim 2 or claim 3 wherein R<sup>11</sup> represents hydrogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy or halogen.

10

          5.     A compound as claimed in any one of claims 2 to 4 wherein R<sup>12</sup> represents hydrogen, C<sub>1-6</sub> alkyl or halogen.

          6.     A compound selected from:

15   2-(4-methoxyphenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;  
     2-(4-fluorophenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;  
     2-(4-methylphenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;  
     2-(3-chlorophenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;  
     2-(2-fluorophenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;  
20   2-(pyridin-2-yl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;  
     2-(4-ethylphenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;  
     2-(2,4-difluorophenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;  
     2-(3,4-dimethylphenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;  
     2-(3-methylphenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;  
25   2-(3-fluorophenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;  
     2-(4-isopropylphenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;  
     2-(4-ethoxyphenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;  
     2-(4-chlorophenyl)-2,5,6,7,8,9-hexahydropyrazolo[4,3-c]cinnolin-3-one;  
     2-(4-methoxyphenyl)-2,5,6,7,8,9,10-heptahydrocyclohepta[c]pyrazolo[4,3-  
30   c]pyridazin-3-one;



2-(4-methylphenyl)-2,5,6,7,8,9,10-heptahydrocyclohepta[c]pyrazolo[4,3-c]pyridazin-3-one;

2-(4-chlorophenyl)-2,5,6,7,8,9,10-heptahydrocyclohepta[c]pyrazolo[4,3-c]pyridazin-3-one;

5 2-(4-fluorophenyl)-2,5,6,7,8,9,10-heptahydrocyclohepta[c]pyrazolo[4,3-c]pyridazin-3-one;

2-(3-methoxyphenyl)-2,5,6,7,8,9,10-heptahydrocyclohepta[c]pyrazolo[4,3-c]pyridazin-3-one;

10 2-(pyridin-2-yl)-2,5,6,7,8,9,10-heptahydrocyclohepta[c]pyrazolo[4,3-c]pyridazin-3-one;

2-(4-methylpyridin-2-yl)-2,5,6,7,8,9,10-heptahydrocyclohepta[c]pyrazolo[4,3-c]pyridazin-3-one;

and salts and prodrugs thereof.

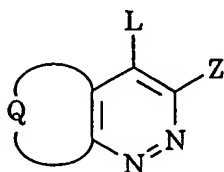
15 7. A pharmaceutical composition comprising a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof or a prodrug thereof in association with a pharmaceutically acceptable carrier.

20 8. The use of a compound as claimed in any one of claims 1 to 6 for the manufacture of a medicament for the treatment and/or prevention of anxiety.

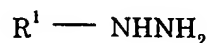
25 9. The use of a compound as claimed in any one of claims 1 to 6 for the manufacture of a medicament for the treatment and/or prevention of convulsions.

10. A process for the preparation of a compound as claimed in claim 1 which comprises:

(A) reacting a compound of formula III with a hydrazine derivative of formula IV, or an acid addition salt thereof:



(III)



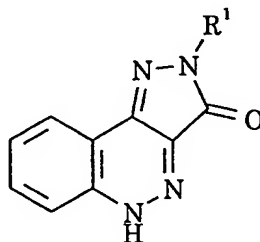
(IV)

5

wherein Q and  $R^1$  are as defined in claim 1, L represents a readily displaceable group, and Z represents a reactive carboxylate moiety; or

(B) reducing a compound of formula VI:

10



(VI)

wherein  $R^1$  is as defined in claim 1; and

15 (C) subsequently, if desired, converting a compound of formula I initially obtained into a further compound of formula I by standard methods.

20 11. A method for the treatment and/or prevention of anxiety which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof or a prodrug thereof.

12. A method for the treatment and/or prevention of convulsions which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in claim 1, or a  
5 pharmaceutically acceptable salt thereof or a prodrug thereof.

# INTERNATIONAL SEARCH REPORT

Intern .al Application No

PCT/GB 98/01774

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D487/04 A61K31/50 //(C07D487/04,237:00,231:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 168 350 A (CIBA-GEIGY) 15 January 1986 see page 20, paragraph 2 - page 21, paragraph 2; claim 1 & US 4 602 014 A (YOKOYAMA) 22 July 1986 cited in the application ---	1,7-9
A	US 4 591 589 A (GASC ET AL) 27 May 1986 cited in the application see claims 1,7 -----	1,7,8



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

7 October 1998

Date of mailing of the international search report

20/10/1998

Name and mailing address of the ISA

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Authorized officer

Alfaro Faus, I

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 98/01774

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11 and 12  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 11 and 12  
are directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/01774

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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US 4591589 A	27-05-1986	NONE	